INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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SHORT ABSTRACT

Oral cancer is a significant global health burden, affecting various regions of the oral cavity, including the gums, lips, tongue, and palate. According to GLOBOCAN 2020, approximately 400,000 new cases and 170,000 deaths were reported annually worldwide. This malignancy is particularly prevalent in South and Southeast Asia, with a high incidence in countries such as Bangladesh, India, Pakistan, and Sri Lanka. In India, oral cancer accounts for nearly one-fourth of the total cancer burden, with higher prevalence among males. The North-Eastern region has emerged as a hotspot for this cancer, primarily due to high tobacco consumption. Despite advancements in therapeutic modalities, challenges such as late-stage diagnosis, high recurrence rates, and poor prognosis persist among patients, highlighting the urgent need for the development of novel therapeutic target.

Hence, the current study investigated the role of Mortalin, a heat shock protein, in oral cancer progression. Mortalin overexpression has been implicated in multiple malignancies, including osteosarcoma, hepatocellular carcinoma, glioblastoma, and breast cancer, where it is associated with poor prognosis. Our analyses demonstrated significant upregulation of Mortalin in oral cancer tissue samples and cell lines, with its expression correlating with advanced disease stages and high tumor grade. Mechanistic studies involving Mortalin knockdown in oral cancer cell lines revealed its role in modulating the Akt/mTOR signaling pathway, along with key regulatory molecules involved in diverse oral cancer hallmarks, such as p53, p-Wee-1, survivin, cyclins, caspases, VEGF-A, matrix metalloproteinases, and cadherins. These findings highlight Mortalin as a potential oncogenic driver in oral cancer, warranting for the targeted therapeutic intervention. Therefore, we further explored the therapeutic potential of Withaferin A (WiA), a bioactive compound derived from *Withania somnifera*, in suppressing Mortalin and oral cancer hallmarks. Interestingly, treatment of oral cancer cells with WiA resulted in Mortalin suppression, accompanied by

inhibition of the Akt/mTOR pathway and key molecules regulating various processes involved in oral cancer progression.

In conclusion, Mortalin emerges as a promising target in oral cancer, and its targeted inhibition by WiA represents a potential therapeutic strategy for the improved management of this disease.